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From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 12 October 2000 (12.10.00)	
International application No. PCT/GB00/00303	**Applicant's or agent's file reference** RJG/2859PCT
International filing date (day/month/year) 02 February 2000 (02.02.00)	**Priority date** (day/month/year) 04 February 1999 (04.02.99)
Applicant LEIGH, Steven et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 August 2000 (30.08.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RJG/JLB/2859 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00303	02/02/2000	04/02/1999

International Patent Classification (IPC) or national classification and IPC
A61K7/00

Applicant
PHARES PHARMACEUTICAL RESEARCH NV et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 16 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/08/2000	29.05.2001

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer
Uhl, M
Telephone No. +49 89 2399 8654

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00303

I. Basis of the r port

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-14	as received on	02/05/2001	with letter of	30/04/2001

Claims, No.:

1-11	as received on	02/05/2001	with letter of	30/04/2001

Drawings, sheets:

1/3-3/3	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-11
	No:	Claims	

2. Citations and explanations
   see separate sheet

R It m V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The subject matter of claims 1-11 of the present application is novel or inventive over the prior art (Art. 33(2) and (3) PCT).

FR-A-2627388 (=D1; cited in the description) discloses a composition comprising acid mucopolysaccharides and a xanthine (caffeine) within a liposome (membrane lipid; structured lipid assembly) in the form of a creme or gel for application onto the skin (see in particular D1; claims 1, 5-10) . In difference to the present application this teaching does not comprise a carboxylic acid, as presently claimed.

EP-A-260241 (=D2; cited in the description) discloses a composition comprising xanthine entrapped within liposomes made from phospholipides and dried to powders (see in particular D2 claim s1,2, 4,5, and 10, 12). Again there is no carboxylic acid comprised in this teaching.

None of the documents renders obvious the compositions as claimed as with a powder comprising at least one membrane lipid and at least one carboxylic acid as biologically active compound, forming a structured lipid assembly (explanation see p.3/4 of the description) when dispersed/dissolved in an aqueous medium.

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
RJG/2859PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 00303	02/02/2000	04/02/1999
Applicant		
PHARES PHARMACEUTICAL RESEARCH NV et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

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   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
[redacted]GB 00/00303

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/00 A61K7/48 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 260 241 A (AKTIEBOLAGET DRACO) 16 March 1988 (1988-03-16) claims 1,2,4,5,10,12 page 3, line 20-23 page 5	1,2,5,6
X	FR 2 627 388 A (ROUSSEL-UCLAF) 25 August 1989 (1989-08-25) claims 1,5-10	1,4-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	02/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
GB 00/00303

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 260241 A	16-03-1988	AU 603139 B	08-11-1990
		AU 7913387 A	07-04-1988
		CA 1256798 A	04-07-1989
		DK 247388 A	06-05-1988
		EP 0282537 A	21-09-1988
		FI 882221 A	11-05-1988
		HU 47840 A,B	28-04-1989
		JP 1500668 T	09-03-1989
		NO 882077 A	11-05-1988
		NZ 221732 A	28-08-1990
		WO 8801862 A	24-03-1988
		ZA 8706641 A	14-03-1988
FR 2627388 A	25-08-1989	BE 1005177 A	18-05-1993
		CH 678011 A	31-07-1991
		DE 3905167 A	31-08-1989
		IT 1230480 B	24-10-1991
		NL 8900383 A	18-09-1989

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International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 7/00, 7/48, A61P 17/00

A1

(11) International Publication Number: WO 00/45774

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(22) International Filing Date: 2 February 2000 (02.02.00)

(30) Priority Data:
9902527.2 4 February 1999 (04.02.99) GB

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(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: MEMBRANE LIPID COMPOSITIONS

(57) Abstract

A composition in the form of a dry powder and which comprises: a) at least one membrane lipid, and b) at least one biologically active compound comprising a xanthine and/or a carboxylic acid, and which forms structured lipid assemblies when dispersed/dissolved in an aqueous medium. A method of preparing such a composition is also provided, together with a dispersion of structured lipid assemblies suspended in a solution of at least one biologically active compound and a method of preparing the same. The compositions and dispersions are suitable for use in creams and lotions for skin care.

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Membrane Lipid Compositions

Field of the invention

The present invention relates to membrane lipid compositions. More specifically, it relates to powder complexes and compositions comprising phospholipid and one or more biologically active compounds, such as a xanthine and/or a salicylate.

Powder compositions of the invention have the unique property to form dispersions comprising structured lipid assemblies (SLAs) suspended in a solution of the active compound. The compositions may be used to deliver the biologically active compound, such as a xanthine and/or a salicylate, to the deeper layers of the skin, more effectively and efficiently, with reduced irritation. By stabilising the active compounds in solution without solvents and strong surfactants, the invention is an improvement on prior art preparations containing xanthine and/or salicylate. The compositions of this invention are employed in lotions, sprays and creams, etc in skin care and other applications.

Background to the invention

Cellulite is a fatty substance produced by fat cells (adipocytes) and deposited mainly under the thighs and buttocks which gives the skin an "orange peel" appearance. Two competing processes involving breakdown (lypolysis) and production (lypogenesis) of fat occur in the cells. In lypolysis, triglycerides are converted into free fatty acids and glycerol by the action of triglyceride lipases. This reaction is activated by cyclic AMP which converts the lipases into active forms. Lypolysis is controlled by phosphodiesterase, an enzyme which breaks down cyclic AMP and effectively prevents lypolysis. Xanthines, such as caffeine, theobromine

and theophylline can inhibit phosphodiesterase and thereby promote lypolysis. These compounds are reported to be active topically and can also temporarily dehydrate cells, making the skin look and feel firmer. Not surprisingly, xanthines are used widely in skin care products and slimming aids to prevent cellulite from accumulating.

Caffeine is a methylxanthine which is a CNS stimulant and inhibitor of phosphodiesterase. It is a white crystalline solid, soluble 1:10 in hot water, but crystallises as fine needles on cooling. It is sparingly soluble in fixed oils and ethanol. The solubility in cold water is approximately 1:50. However it is soluble 1:10 in equal parts of ethanol and water. Topical preparations containing caffeine are commonly used in anti-cellulite treatments. The preparations are either hydro-alcoholic solution/gel or cream/lotion type products. There are problems relating to irritancy or reduced efficacy with both of these types of formulations. An effective amount of caffeine cannot be kept in solution without using large amounts of ethanol. If a large amount of ethanol is used, the solution dries rapidly, leaving a white powder on the skin after application. Creams and lotions are more cosmetically acceptable, but they are perceived to be less effective because of the smaller amount of caffeine that can be solubilised. Therefore there is a need for an aesthetic and cosmetically acceptable preparation containing an effective amount of caffeine which does not crystallise out, is non-irritant and does not dry out the skin.

Salicylic acid is used in topical applications as an exfoliating agent and to remove wrinkles from under the eyes, in low concentrations(<0.2%), often as alkali salt. It is soluble in ethanol but only sparingly soluble in water. Salicylates, and in particular, salicylic acid is a skin irritant and it is usually combined with emollients in skin care products.

In this specification, the term phospholipid refers to at least one membrane

lipid or, preferably, a mixture of membrane lipids comprising phosphatidyl choline (PC), phosphatidyl ethanolamine (PE), phosphatidyl inositol (PI), phosphatidic acid (PI) and/or phosphatidyl serine (PS). The definition includes diacyl phospholipids and their monoacyl equivalents, with either unsaturated or saturated hydrocarbon chain(s). Phospholipids are the most common examples of natural membrane lipids. They are the natural building blocks of cell membranes. Membrane lipids are essential for normal skin function. They protect the skin from irritants and alleviate the irritation. Therefore membrane lipids are commonly used in skin care preparations to confer emollient and protective functions and to control transepidermal water loss. Most commonly, they are used to form liposomes designed to carry active compounds. Liposomes are made up of one or more alternating bilayers which can sequester both oil soluble and water soluble compounds. Liposomes have poor long term storage stability, and therefore there are serious limitations in utilising liposomes to carry active compounds.

The present invention does not depend on liposome structure to entrap the active compound. It is not concerned with formation of liposomes, or with liposome entrapment. The compositions simply utilise phospholipids, particularly mixtures of diacyl and monoacyl phospholipids, to prepare easily dispersible powder compositions that form small structured lipid assemblies (SLAs) on contact with water. The SLAs may be vesicles, micelles, mixed micelles or often a heterogeneous mixture, depending on the types of phospholipid used. Typically, the SLAs have a diameter of between 0.05μ to 1μ (i.e. from 50nm to 1000nm). Surprisingly, it has been found that SLAs offer a valuable and effective source of natural membrane lipids that is convenient and easy to assimilate into the skin structure. The fact that the SLAs can also transport dissolved biologically active compounds is an unexpected bonus.

On p1651 of the 31st edition of Martindale The Extra Pharmacopoeia, it is disclosed that caffeine can be dissolved in concentrated solutions of alkali benzoates and salicylates. Caffeine is used orally in medicine as a CNS stimulant. It is also included in analgesics as the free base or as a water-soluble (e.g. citrate) salt. However, in skin care applications, the free base is mostly preferred due to its lipophilic properties.

There are many known caffeine preparations for anti-cellulite treatment. These contain a maximum of about 5% caffeine dissolved in ethanol or incorporated in the form of caffeine benzoate in creams and lotions.

PCT application WO 95/34279 describes aqueous liposomal dispersions of phospholipids comprising a carboxylic acid or salicylic acid in the salt form that claim to be non-irritant and have skin beneficial properties. It would appear, from the examples disclosed, that the liposome suspensions are made from a pro-liposome composition disclosed in EP 0 158 441 B1.

Summary of the invention

The object of the present invention is two fold. Firstly, to provide a novel dry powder composition comprising at least one membrane lipid (e.g. phospholipid) with at least one biologically active compound (namely a xanthine, e.g. caffeine, and/or a carboxylic acid, e.g. alkali salicylate/salicylic acid), and which forms structured lipid assemblies (SLAs) when dispersed/dissolved in an aqueous medium, such as water. Secondly, to provide a stable dispersion of SLAs *in situ*, suspended in a solution of the biologically active compound(s). The dispersion may be made by using either the dry powder complex or by incorporating (dispersing/dissolving) the components thereof individually in water or other aqueous medium. Creams, gels, lotions, sprays and other preparations formulated for topical administration may be prepared from the dispersion or suspension accordingly.

In the compositions of this invention which contain them both, the efficacy of caffeine is enhanced because it is in molecular solution with the salicylate. Most importantly, the invention harnesses the properties of phospholipids to improve the bioavailability and reduce the irritancy of biologically active compounds, in a physically stable complex. Furthermore, the method of this invention avoids the use of solvents or harsh surfactants which can irritate and damage the skin. This represents a significant improvement on prior art preparations containing a xanthine and/or a carboxylic acid. Compositions comprising phospholipid, caffeine and/or salicylate in a dry powder complex have not been disclosed in the prior art.

Description of preferred embodiments

A preferred embodiment of the invention is a powder composition comprising the components in a homogeneous mixture. The preferred xanthine is caffeine as the free base, but other xanthines such as aminophilline, theophylline and theobromine may also be used. The proportion of caffeine in the powder complex is preferably between 10% to 80%, more preferably between 40% to 70%, by weight.

Sodium salicylate/salicylic acid, a β-hydroxycarboxylic acid, is the preferred carboxylic acid but other alkali salicylates or benzoates may be used. Benzoates tend to be more sensitising and should therefore be used with caution. The amount of sodium salicylate by weight in the powder mixture is preferably between 10% to 50%, more preferably between 20% to 40%. In addition to or in place of salicylates, α-hydroxycarboxylic acids, e.g. glycollic acid, lactic acid, citric acid, tartaric acid, maleic acid or mandelic acid, and/or α-ketocarboxylic acids, e.g. pyruvic acid, including their salt forms may be used in about the same proportions, i.e. about 10% to about 50% by weight, with the pH of the final preparation adjusted to between pH

5 to 7.5, so as to give maximum performance and minimum irritancy. The α-hydroxy carboxylic acids are found in fruit extracts and are known as "fruit acids". They are commonly used in anti-wrinkle preparations due to their keratolytic and anti-oxidant properties. It will be understood that the products of this invention may contain one, two, three or more biologically active compounds.

In another preferred embodiment of the invention, in place of caffeine at least one carboxylic acid or salt, eg, salicylate, is used in combination with the lipid to counteract the irritant potential of the fruit acids. These compositions are particularly suitable in anti-wrinkle skin care preparations. Where only two components, e.g. phospholipid and one carboxylic acid or acid salt, are present in the powder composition, the weight ratio of lipid to biologically active compound is 20:1 to 1:20, preferably 10:1 to 5:1, with the proviso that there is sufficient lipid in the powder mixture to yield SLAs, when the powder mixture is dispersed in water at about 60°C.

The second essential component is a membrane lipid, and this may include natural, hydrogenated and synthetic phospholipids, glycolipids and polyglycerol esters. Blends of diacyl or monoacyl phospholipid available commercially as lecithin and enzyme hydrolysed lecithin, with a total phospholipid content of at least 60%, are preferred. Diacyl phospholipids, e.g. PC, tend to form SLAs which may be bilayered lamellae structures with an average diameter of about 1μ in water, whilst monoacyl phospholipids (MAPC) form micelles that are about 50nm average diameter. Mixed micelle systems are formed by combinations of PC and MAPC and the average particle size is somewhere in between the diameters quoted above. Most preferably, the phospholipids are in particulate or granular form. The quantity of lipid in the dry powder mixture varies between 5% to 70%, most preferably between 10% to 50%. A combination of unsaturated lipid with low phase transition temperature (Tc) and hydrogenated lipid with

higher Tc is preferred to obtain complexes with optimum properties.

There are several benefits in using phospholipids in the invention. In skin care products, they can replace natural lipid and function as natural moisturisers, counteract the dehydrating effect of caffeine, and alleviate the irritant potential of the fruit acids. Phospholipids are also known to increase the bioavailability of biologically active compounds. Furthermore, phospholipids stabilise the formulations, preventing any mild crystal growth of e.g. caffeine, if the preparations are stored at low temperatures. This effect can be seen when two formulations are prepared, one containing a high level of caffeine without lipid, the other containing caffeine and lipid complex. When stored at 4°C, crystals develop much faster in the preparation without lipid. Phospholipids are natural emulsifiers and can help stabilise up to 40% of an oil and thereby reduce the amount of ethoxylated emulsifiers. A further advantage of the invention is that the phospholipid helps to bind and prevent segregation of the components in the powder mixture, particularly during storage and transport.

The powder compositions may be prepared by dissolving/dispersing all the components in a suitable solvent, e.g. ethanol, aqueous ethanol solutions or chloroform and removing the solvent to obtain a solid complex that can be pulverised. Alternatively, all the components may be simply mixed or milled together to obtain a homogeneous and uniform powder mixture. This offers a convenient and efficient means to utilise caffeine and/or salicylate in a form which can be incorporated into different types of formulations. The powder mixture is simply added to water or other aqueous medium to obtain, *in situ,* a soluble caffeine and/or salicylate complex in a dispersion of lipid particles, free from ethanol. The suspension may be used as a sprayable lotion or it may be used to prepare creams and lotions that can additionally contain up to 40% of an oil.

The lipid-caffeine powder complex is a homogeneous composition with a mean particle size between 0.1 mm to about 5 mm in diameter. Preferably, the mean diameter is about 200μ to 500μ. The compositions have good storage stability and can be kept for extended periods until required.

In a further embodiment of the invention, the individual components, namely phospholipid and the biologically active compound(s) e.g. caffeine and/or salicylate, are added separately in pre-weighed amounts, to water or other aqueous medium. The resulting dispersion of SLAs can be used in the preparation of a cream or a lotion. The order is not critical, although preferably, the salicylate should be added first, followed by the caffeine or other xanthine. The lipid, which should preferably be in particulate form, is added last to the solution, with stirring, at an elevated temperature below about 60°C. The phospholipids additionally help to keep the caffeine/salicylate in solution, most likely in a molecular complex. The mole ratio of caffeine to salicylate in the solution is between 1:1 to 1:4, preferably about 1:2. There is no strict limit to the ratio of caffeine to lipid, but preferably it should lie within the range 20:1 to 1:20, preferably 10:1 to 5:1.

The invention will be further described in the following examples. All percentages are by weight unless otherwise indicated.

Example 1

Caffeine	52.6 %
Salicylic acid (Na salt)	26.3 %
*Phospholipid	21.1 %

* Mixture of suitable lipid blends, containing a minimum of 60% total phospholipids

comprising PC, PE, PA, PI, and glycolipids in particulate form. In the above example the lipid blend was made up of a 1:2 mixture of hydrogenated and unsaturated lipids.

Method: 500 gm of the lipid-caffeine powder complex was prepared in the laboratory by grinding all the components in a mortar and pestle until a homogeneous and uniform powder composition was obtained. One gm of the powder composition dispersed in 10ml of water at 60°C to yield a solution of caffeine and SLAs in suspension, comprising vesicular structures of about 1μ Z average diameter, as seen in the accompanying electron micrograph of Fig 1A.

Example 2

Caffeine	58.8 %
Salicylic acid (Na salt)	29.4 %
*Phospholipid	11.8 %

*Similar blend as in Example 1.

10 gm of the components was dissolved in 90% ethanol at about 50°C in a closed container. The ethanol was evaporated off to obtain a hard powder lump which could be comminuted to a free flowing powder of about 500 micron average diameter.

Example 3

Caffeine	64.8 %
Salicylic acid (Na salt)	24.9%
*Phospholipid	10.3 %

*Enyme modified lecithin containing about 65% MAPC and 15%PC.

10 kg of the lipid-caffeine powder complex was prepared by coarse mixing, followed by size reduction through a screen in a hammer mill, to obtain a free flowing uniform powder composition. Alternatively, the three

components could have been dissolved in ethanol-water solution and dried to a powder. One gm of the powder dispersed in 10 ml of warm water to give a clear micellar solution of caffeine and SLAs, as seen in the electron micrograph of Fig 1B (where no vesicular structures can be discerned).

Example 4

Salicylic acid (Na salt)	50.0 %
*Phospholipid	50.0 %

*Hydrogenated lipid containing about 60% of total phospholipids and glycolipids.

The two components were co-milled to obtain a free flowing uniform lipid-salicylate powder composition that readily disperses in water at about 60°C with minimum agitation, to form a homogeneous dispersion of discrete SLAs and dissolved salicylate. In place of salicylate, one or more alpha hydroxycarboxylic acids (AHA) e.g. citric acid or maleic acid or their salt forms may be used.

The invention also relates to the use of the aforementioned lipid powder compositions for preparing suspensions, lotions and creams containing caffeine and/or a carboxylic acid/salt. Typical examples of the preparations are further described below.

Example 5

The lipid-caffeine powder from Example 1 was used to prepare an oil in water (o/w) cream.

Lipid-caffeine complex 7%

Emulgade SEV	5% w/w
Cetyl alcohol	2%
Dicaprylyl ether	4%
Oleyl erucate	1%

Decyl oleate	2%
Cocoglycerides	3%
Glycerol	3%
Preservative	0.2%
Fragrance	0.2%
Water	ad 100%

The emulsifier (Emulgade) was obtained from Henkel. The lipid-caffeine powder from Example 1 was dispersed in about half the total amount of water at about 60°C. The emulsifier and waxes were melted in the mixture of oils heated to about 65°C and added to the aqueous suspension of caffeine, with stirring to form a cream. The rest of the water at 60°C was added to obtain an o/w lipid-caffeine cream. The cream was homogenised and cooled to room temperature. It was packed into jars. After storage for 30 days at 0°C and 45°C, the cream was examined at room temperature, for crystal growth. No crystals can be seen under a light microscope (at magnification of about x100), as shown in Fig 2A (which shows a sample of the cream according to this example after storage at 0°C for 30 days). Fig 2B shows a sample of a cream prepared as a control (containing caffeine but no lipid) after storage at 0°C for 30 days; crystals have clearly developed.

Example 6

The lipid-caffeine powder complex from Example 2 was used to prepare the gel formulation in this example.

Lipid-caffeine complex	6%
Glycerol	3%
Carbopol 940	0.4%
Permulant TR-1	0.2%

Cetearyl isononanate		3%
Tocopherol acetate		0.05%
Preservative		0.2%
Fragrance		0.2%
Water	ad	100%

The Carbopol (a gelling agent) and Permulant (a thickener) were hydrated and dissolved in about half quantity of water at about 60°C, with high speed stirring, to obtain a lump free solution. The rest of the ingredients, except for the lipid-caffeine complex and the fragrance, were added. The lipid-caffeine complex was dispersed in the rest of the water at about 65°C to form a homogeneous lipid suspension and added to the Carbopol solution. The suspension was adjusted to pH 6.5 –7.0 to obtain a gel preparation comprising discrete SLAs and solubilised caffeine.

Example 7

This is an example of a simple lotion containing SLAs and solubilised caffeine prepared from the lipid-caffeine complex according to Example 3.

Lipid-caffeine complex		8%
Preservative		0.2%
Fragrance		0.2%
Water	ad	100%

The lipid-caffeine powder was added to water at ambient temperature containing the preservative, with mild agitation. A totally transparent micellar solution of SLAs with Z average diameter of below about 60nm was obtained using a Malvern autosizer. The fragrance was added last.

In place of the lipid-caffeine complex from Example 3, two gm of the lipid-

salicylate complex from Example 4 was added to the water containing the preservative at about 65°C, with agitation, to prepare a translucent lotion containing SLAs suspended in caffeine solution. The fragrance was added at room temperature. The Z average particle diameter of the SLAs was about 1μ, using a Malvern autosizer laser.

The powder complexes in Examples 1 to 4 are typical examples. Similar powder complexes may be prepared by using different blends of phospholipids and other xanthines and carboxylic acids. Alternatively, the xanthine may be omitted and a powder complex comprising phospholipid and one or more fruit acids or one or more α-ketocarboxylic acids may be obtained using similar methods. In this case, the amount of fruit acid used in the powder mixture may vary from 10% to 50% by weight. The resultant powder compositions may be formulated into creams and lotions which are typically shown in Examples 5 to 7.

CLAIMS

1. A composition in the form of a dry powder and which comprises:

a) at least one membrane lipid, and

b) at least one biologically active compound comprising a xanthine and/or a carboxylic acid,

and which forms structured lipid assemblies when dispersed/dissolved in an aqueous medium.

2. A composition as claimed in claim 1, wherein said membrane lipid comprises a phospholipid or mixture of phospholipids.

3. A composition as claimed in any one of the preceding claims, wherein said biologically active compound comprises an α-hydroxycarboxylic acid, a β-hydroxycarboxylic acid and/or an α-ketocarboxylic acid.

4. A composition as claimed in any one of the preceding claims, wherein said biologically active compound is caffeine and/or salicylate or pharmaceutically acceptable salts thereof.

5. A composition as claimed in any one of the preceding claims, wherein the proportion of said membrane lipid to said biologically active compound is from 1:20 to 20:1 by weight.

6. A method of preparing a composition as claimed in any one of the preceding claims, which comprises either mixing or milling together the components to produce a homogeneous dry powder, or dispersing/dissolving the components, either sequentially or simultaneously, in a solvent, subsequently removing the said solvent so as

to form a solid mixture and then pulverising the said solid mixture to produce a homogeneous dry powder.

7. A dispersion of structured lipid assemblies suspended in a solution of at least one biologically active compound which comprises a xanthine and/or a carboxylic acid.

8. A method of preparing a dispersion of structured lipid assemblies as claimed in claim 7, which comprises dispersing/dissolving a dry powder composition as claimed in any one of claims 1 to 5, or the components of such a composition, with the said components being dispersed or dissolved either sequentially or simultaneously, in an aqueous medium.

9. A dispersion as claimed in claim 7 or as prepared by the method of claim 8, and which is in the form of a cream, gel or lotion formulated for topical administration.

FIG. 1A

FIG. 1B

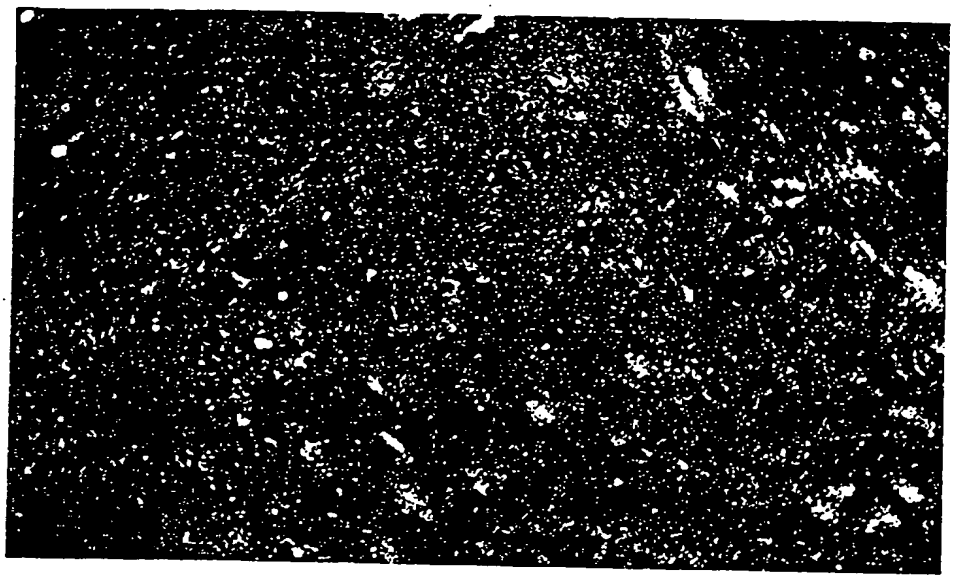

FIG. 2A

FIG. 2B

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/00 A61K7/48 A61P17/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 260 241 A (AKTIEBOLAGET DRACO) 16 March 1988 (1988-03-16) claims 1,2,4,5,10,12 page 3, line 20-23 page 5	1,2,5,6
X	FR 2 627 388 A (ROUSSEL-UCLAF) 25 August 1989 (1989-08-25) claims 1,5-10	1,4-9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	02/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		IT 1230480 B	24-10-1991
		NL 8900383 A	18-09-1989

INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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X	FR 2 627 388 A (ROUSSEL-UCLAF) 25 August 1989 (1989-08-25) claims 1,5-10	1,4-9

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"O" document referring to an oral disclosure, use, exhibition or other means

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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Peeters, J

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ATTACHMENT D

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		DK 247388 A	06-05-1988
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		FI 882221 A	11-05-1988
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		JP 1500668 T	09-03-1989
		NO 882077 A	11-05-1988
		NZ 221732 A	28-08-1990
		WO 8801862 A	24-03-1988
		ZA 8706641 A	14-03-1988
FR 2627388 A	25-08-1989	BE 1005177 A	18-05-1993
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		IT 1230480 B	24-10-1991
		NL 8900383 A	18-09-1989

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(54) Title: MEMBRANE LIPID COMPOSITIONS

(57) Abstract

A composition in the form of a dry powder and which comprises: a) at least one membrane lipid, and b) at least one biologically active compound comprising a xanthine and/or a carboxylic acid, and which forms structured lipid assemblies when dispersed/dissolved in an aqueous medium. A method of preparing such a composition is also provided, together with a dispersion of structured lipid assemblies suspended in a solution of at least one biologically active compound and a method of preparing the same. The compositions and dispersions are suitable for use in creams and lotions for skin care.

ATTACHMENT C